

PCT

**WORLD INTELLECTUAL PROPERTY ORGANIZATION**  
**International Bureau**



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> :  C07K 14/00		A2	(11) International Publication Number:  WO 00/24774
			(11) International Publication Number:  4 May 2000 (04.05.00)
(21) International Application Number:		PCT/US99/25458	
(22) International Filing Date:		28 October 1999 (28.10.99)	
(30) Priority Data:			
09/181,711	28 October 1998 (28.10.98)	US	(71) Applicant (for all designated States except US): INCYTE PHARMACEUTICALS, INC. [US/US]; 3174 Porter Drive, Palo Alto, CA 94304 (US).
Not furnished	28 October 1998 (28.10.98)	US	
09/209,547	11 December 1998 (11.12.98)	US	
Not furnished	11 December 1998 (11.12.98)	US	
09/313,457	17 May 1999 (17.05.99)	US	
Not furnished	17 May 1999 (17.05.99)	US	
(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications			
US	09/209,547 (CIP)		
Filed on	11 December 1998 (11.12.98)		
US	09/313,457 (CIP)		
Filed on	17 May 1999 (17.05.99)		
US	09/181,711 (CIP)		
Filed on	28 October 1998 (28.10.98)		
US	Not furnished (CIP)		
Filed on	28 October 1998 (28.10.98)		
US	Not furnished (CIP)		
Filed on	11 December 1998 (11.12.98)		
US	Not furnished (CIP)		
Filed on	17 May 1999 (17.05.99)		
		(72) Inventors; and	
		(75) Inventors/Applicants (for US only): TANG, Y., Tom [CN/US];	
		4230 Ranwick Court, San Jose, CA 95118 (US). YUE, Henry [US/US]; 826 Lois Avenue, Sunnyvale, CA 94087 (US). HILLMAN, Jennifer, L. [US/US]; 230 Monroe Drive #12, Mountain View, CA 94040 (US). CORLEY, Neil, C. [US/US]; 1240 Dale Avenue #30, Mountain View, CA 94040 (US). GUEGLER, Karl, J. [CH/US]; 1048 Oakland Avenue, Menlo Park, CA 94025 (US). BAUGHN, Mariah, R. [US/US]; 14244 Santiago Road, San Leandro, CA 94577 (US). AU-YOUNG, Janice [US/US]; 1419 Kains Avenue, Berkeley, CA 94702 (US).	
		(74) Agents: BILLINGS, Lucy, J. et al.; Incyte Pharmaceuticals, Inc., 3174 Porter Drive, Palo Alto, CA 94304 (US).	
		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
		<b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>	

(54) Title: GROWTH FACTOR RELATED MOLECULES

1	M R G T R I L A L L A L V L A - - - A C G E L A P A L R C Y V	2777282
1	M A S R W A V Q L L L V A A W S M G C G E - - - A L K C Y T	GI 1536902
28	C P E P T G V S D C V T I A T C T T N E T M C K T T L Y S R	2777282
28	C K E P M T S A S C R T I T R C K P E D T A C M T T L V T V	GI 1536902
58	E I V Y P F O G D S T V T K S C A S K C K P S D V D G I G O	2777282
58	E A E Y P F N Q S P V V T R S C S S S C V A T D P D S I G A	GI 1536902
88	T L P V S C C N T E L C N V D G A P A L N S L H C G A L T L	2777282
88	A H L I F C C F R D L C N S E - - - - - - - - - - - - - - -	GI 1536902
118	L P L L S L R L	2777282
103	- - - - - - - - - L	GI 1536902

## (57) Abstract

The invention provides human growth factor related molecules (GFRP) and polynucleotides which identify and encode GFRP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of GFRP.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						





(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(88) Date of publication of the international search report:  
28 December 2000

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

**Published:**

— With international search report.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/25458

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C12N5/10 C12N15/63 C07K14/475 C07K16/22  
A61K38/18

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 99 46281 A (GENENTECH, INC.) 16 September 1999 (1999-09-16) page 41, line 25 -page 42, line 4 page 157, line 20 - line 30; figures 184,185; example 74 ---	1-16,19
X	MARRA, M. ET AL.: "The WashU-HHMI mouse EST project" EMBL DATABASE, EMEST36.MMAA59621; ACCESSION-N0.: AA259621, 19 March 1997 (1997-03-19), XP002140754 the whole document	1-6,9-13
Y	---	7,8, 14-16

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&amp;\* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

21 June 2000

14.09.00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Donath, C

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/25458

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SOARES, M.B.: "Program for rat gene discovery and mapping" EMBL DATABASE, EMEST6.AI112088; ACCESSION-N0.: AI112088, 4 September 1998 (1998-09-04), XP002140755 the whole document	1-6,9-13
Y		7,8, 14-16
A	RIDGE, R.J. AND SLOANE, N.H.: "Partial N-terminal amino acid sequence of the anti-neoplastic urinary protein (ANUP) and the anti-tumour effect of the N-terminal nonapeptide of the unique cytokine present in human granulocytes" CYTOKINE, vol. 8, no. 1, January 1996 (1996-01), pages 1-5, XP000915567 cited in the application the whole document	1,2,15, 16,19
A	BRANDT R. ET AL.: "Identification and biological characterization of an epidermal growth factor-related protein: Cripto-1" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 269, no. 25, 24 June 1994 (1994-06-24), pages 17320-17328, XP000910201 the whole document	-----

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 99/25458

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
**Although claim 19 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.**
2.  Claims Nos.: **17, 18, 20**  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
**see FURTHER INFORMATION sheet PCT/ISA/210**
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See additional sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
**1 - 20 (partially)**

#### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Continuation of Box I.2

Claims Nos.: 17,18,20

Claims 17 and 18 concern an agonist and an antagonist of GFRP-1, respectively. Claim 20 concerns a method which makes use of the antagonist of GFRP-1. The agonist or the antagonist of GFRP-1. The agonist and antagonist are only defined by the method which can be used in order to identify these compounds. Since it is completely unclear which kind of substances will be identified by the respective method and since in the specification no concrete examples for these kind of substances are given, the scope of said claims is totally ambiguous and undefined. Moreover, it cannot be excluded that even substances known in the art may be recognized as agonists or antagonists of GFRP-1.

In view of the wording of the claims presently on file, which render it difficult, if not impossible, to determine the matter for which protection is sought, the present International application fails to comply with the clarity requirements of Article 6 PCT to such an extent that a meaningful search of the claims is impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear, namely claims 1-16 and 19 (all partially).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-20 (partially)

Claims 1-20 (partially) refer to a purified human growth factor related molecule (GFRP-1) comprising the amino acid sequence as shown in SEQ ID NO:1 and the polynucleotide encoding said GFRP-1. GFRP-1 is 125 amino acids in length and has chemical and structural similarity with ANUP and with mouse ARS component B precursor. Furthermore, the claims concern expression vectors, host cells, antibodies, agonists, antagonists, and methods for diagnosing, treating or preventing disorders associated with expression of GFRP-1.

2. Claims: 1-20 (partially)

Claims 1-20 (partially) refer to a purified human growth factor related molecule (GFRP-2) comprising the amino acid sequence as shown in SEQ ID NO:2 and the polynucleotide encoding said GFRP-2. GFRP-2 is 127 amino acids in length and has chemical and structural similarity with hTECK, with human Dvic-1 C-C chemokine, and with mouse CC chemokine ALP. Furthermore, the claims concern expression vectors, host cells, antibodies, agonists, antagonists, and methods for diagnosing, treating or preventing disorders associated with expression of GFRP-2.

3. Claims: 1-20 (partially)

Claims 1-20 (partially) refer to a purified human growth factor related molecule (GFRP-3) comprising the amino acid sequence as shown in SEQ ID NO:3 and the polynucleotide encoding said GFRP-3. GFRP-3 is 147 amino acids in length and has chemical and structural similarity with chicken follistatin and with human follistatin-related protein FLRG. Furthermore, the claims concern expression vectors, host cells, antibodies, agonists, antagonists, and methods for diagnosing, treating or preventing disorders associated with expression of GFRP-3.

4. Claims: 1-20 (partially)

Claims 1-20 (partially) refer to a purified human growth factor related molecule (GFRP-4) comprising the amino acid sequence as shown in SEQ ID NO:4 and the polynucleotide encoding said GFRP-4. GFRP-4 is 345 amino acids in length and has chemical and structural similarity with human BMP-1 and with chicken BMP-1. Furthermore, the claims concern expression vectors, host cells, antibodies, agonists, antagonists, and methods for diagnosing, treating or preventing disorders associated with expression of GFRP-4.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/25458

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9946281	A 16-09-1999	AU	3072199 A	27-09-1999
		AU	3075099 A	11-10-1999
		WO	9947677 A	23-09-1999
		AU	1532499 A	15-06-1999
		EP	1032667 A	06-09-2000
		WO	9927098 A	03-06-1999
		AU	3757099 A	08-11-1999
		WO	9954467 A	28-10-1999
		AU	1070399 A	10-05-1999
		EP	1025227 A	09-08-2000
		WO	9920756 A	29-04-1999